REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-25 are in the case.

I. KRALOVANSZKY AND CALABRESI REFERENCES

On pages 3 and 4 of the action, the Examiner has requested that Kralovanszky and Calabresi be submitted with an IDS. In response, an IDS with a PTO 1449 listing those two references together with a copy of each of the references is attached to the present response.

II. OBVIOUSNESS-DOUBLE PATENTING REJECTIONS

Claims 1-25 stand rejected on obviousness-type double patenting grounds as allegedly constituting obviousness-type double patenting over claims 1-26 of U.S. patent 5,968,914. Claims 1-25 also stand rejected on obviousness-type double patenting grounds as allegedly constituting obviousness-type double patenting over claims 48-74 of copending application Serial No. 08/473,332. It is requested that the obviousness-type double patenting rejections be placed in abeyance until the outcome of prosecution of the claims alleged to give rise to obviousness-type double patenting is known.

III. THE OBVIOUSNESS REJECTIONS

A. NONOBVIOUS OVER MARTIN, SOMMADOSSI, VON BORSTEL AND FALCONE

Claims 1-15, 18-19 and 22-25 stand rejected under 35 USC 103 as being allegedly unpatentable over Martin et al or Sommadossi et al when taken in view of Von Borstel et al (WO 89/03837) and Falcone. The rejection is traversed for the following reasons.

The invention of the present application is directed to a method for the prevention or treatment of toxicity due to a pyrimidine nucleoside analog. The method comprises the steps of administering to an animal a pharmaceutically effective amount of an acyl derivative of a non-methylated pyrimidine nucleoside.

As admitted in the action (page 7), neither Martin nor Sommadossi suggests the use of acylated uridine or cytidine derivatives. In an attempt to cure this deficiency, the Examiner relies on Von Borstel '837 and asserts that it would have been obvious to a person of ordinary skill to have substituted acylated uridine or cytidine as described by Von Borstel in place of the free uridine disclosed by Martin and Sommadossi in order to increase serum and tissue levels of uridine and thereby reduce toxicity of 5-FU or AZT or any other pyrimidine nucleoside analog, regardless of the chemotherapeutic target of the nucleoside analog. Applicants disagree for the following reasons.

Martin (and others, e.g. Peters et al (Brit. J. Cancer 57:259-265, 1988)) disclose the use of uridine to reduce toxicity of 5-fluorouracil. This permits 5-FU dose escalation and a consequent net improvement in antitumor efficacy.

However, Falcone (discussed in more detail below) discloses that raising levels of uridine in the plasma higher than those achieved by low-dose uridine alone or BAU alone does not result in any improvement in counteracting AZT toxicity. Contrary to the rejection, therefore, based on Falcone one of ordinary skill would not have been motivated to embark on an approach of therapy wherein uridine plasma levels are increased above the levels attainable by administering non-acylated uridine.

In addition, **unexpected** results have been obtained according to the present invention when acyl derivatives of uridine of the invention, e.g. 2',3',5'-triacetyluridine (TAU), are administered orally in conjunction with 5-FU. This is discussed in the specification at pages 42-44 and Example 6. Neither Martin nor Peters was able to induce even partial (50%) regressions of the murine adenocarcinoma colon 26 with high-dose 5-FU alone at the maximum tolerated dose (100 mg/kg/week). In contrast, high-dose 5-FU in combination with oral TAU consistently results in a high incidence (60-80%) of complete regressions of established tumors.

Moreover, Kralovanszky et al (Cancer Chemother Pharmacol 1993; 32:243-8) (further copy attached) report that uridine administration after 5FU does not reduce the severity of gastrointestinal activity due to 5FU, although it does accelerate recovery from GI damage. In contrast, in human clinical trials with oral TAU administered after high dose 5FU, there is a remarkable reduction of gastrointestinal damage indicated by the no grade 3 or grade 4 mucositis or diarrhea in patients receiving up to 100 mg/m^2 5FU per week (Kelsen et al, Journal of Clinical Oncology (April 1997)15(4);1511-1517, submitted with the IDS dated May 22, 2002). Thus, acyl derivatives of pyrimidine nucleosides provide **unexpected** benefits beyond those that have been reported for

parenteral or oral administration of uridine when used to modify the toxicity and efficacy of antineoplastic pyrimidine nucleoside analogs. These same unexpected benefits are observed when TAU is administered with an inhibitor or uridine phosphorylase, e.g. benzolyoxybenzylacyclouridine, but not when the uridine phosphorylase inhibitor alone is administered (M. el Kouni, unpublished results).

Von Borstel '837 describes methods of delivering acyl derivatives of uridine or cytidine for the treatment of cardiac insufficiency, myocardial infarction, cirrhosis of the liver, cerebrovascular disorders, respiratory distress syndromes and diabetes. The methodology as specifically claimed in the present application is in no way disclosed or suggested by Von Borstel, either when taken alone or in combination with Martin and/or Sommadossi and Falcone.

Claims 18-19 are directed to a method for preventing or treating toxicity due to a pyrimidine nucleoside analog (e.g. AZT) comprising administering to an animal an acylated derivative of uridine, deoxyuridine or cytidine; and an inhibitor of uridine phosphorylase. As conceded on page 8 of the action, neither Martin, Sommadossi nor Von Borstel teaches the use of an inhibitor of uridine nucleoside phosphorylase. The Examiner relies on Falcone, et al., Blood (1990) 76(11): 2216-2221 as a disclosure relating to the use of an inhibitor of uridine nucleoside phosphorylase, benzylacylouridine (BAU), to increase the serum and tissue levels of free uridine, thereby reducing the toxicity of AZT. Based on Falcone, in combination with the Martin, Sommadossi and von Borstel publications, it is alleged that it would have been obvious to administer acylated uridine or cytidine in combination with a uridine phosphorylase

inhibitor to obtain the combined uridine elevating effects of two compounds known in the art to increase the bioavailability of free uridine. This position is respectfully traversed.

To make out *a prima facie* case of obviousness, it is not sufficient that the teaching of the prior art could have been modified to arrive at the claimed invention. Rather, the USPTO bears the burden of establishing that there was **motivation**, based on the prior art, to do so. As stated by the CAFC in *In re Vaeck*:

> "Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should... carry out the process; and (2) whether the prior art would also have revealed that in so... carrying out, those of ordinary skill would have a reasonable expectation of success.... Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991) (internal citations omitted)

The Examiner asserts on page 8 of the action that the uridine elevating effects of a uridine phosphorylase inhibitor provide the motivation to combine such an inhibitor with an acylated uridine or cytidine. This is not the case.

As is clear from Falcone et al., a person of ordinary skill in the art would **not** have been motivated to combine an inhibitor of uridine phosphorylase with a source of uridine in order to prevent or treat toxicity due to a pyrimidine nucleoside analog. Falcone teaches that the increased *in vivo* levels of uridine resulting from such combination did not result in reductions in AZT toxicity as compared to the uridine phosphorylase inhibitor BAU alone or uridine alone. This can be seen from Falcone, et al., which states:

> "Indeed, our present observation that BAU doses above 300 mg/kg/d, or combinations of BAU with low doses of exogenous Urd, do not result in improved therapeutic efficacy as compared with BAU alone (300 mg/kg/d) supports

> previous in vitro observations that the maximum ability of exogenous Urd to reverse AZT cytotoxicity is achieved at the relatively low Urd concentration of 50 μmol/L." (Falcone, et al., paragraph bridging pp. 2219-2220)

Based on the above-quoted passage from Falcone, the person of ordinary skill in the art would **not** have expected that the combination of a uridine phosphorylase inhibitor (such as BAU) and a source of uridine would result in improved efficacy in preventing or treating toxicity due to a pyrimidine nucleoside analog compared to either the uridine phosphorylase inhibitor alone or the source of uridine alone. Falcone would have led the person of ordinary skill in the art to expect that high plasma levels of uridine, however achieved, are no more effective than relatively lower plasma levels of uridine in counteracting the toxic effects of a pyrimidine nucleoside analog such as AZT. The person of ordinary skill in the art would not have had the reasonable expectation of success necessary to sustain a *prima facie* case of obviousness.

B. NONOBVIOUS OVER BHALLA, VON BORSTEL, AND HANZE

Claims 16-17 and 20-21 stand rejected under 35 USC 103 as allegedly unpatentable over Bhalla et al when taken in view of Von Borstel (WO 89/03838) and U.S. patent 4,017,606 to Hanze. That rejection is traversed for the following reasons.

Claims 16-17 are directed to a method for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering a pharmaceutically effective amount of triacetylcytidine (claim 16) or diacetyldeoxycytidine (claim 17). The rejection of claim 16 is based on a mischaracterization of the invention. The rejection stated that claim 16 is "directed to a method . . . comprising the administration of . . . an acylated

deoxycytidine." (Office Action, page 8). Contrary to the assertion in the rejection, triacetylcytidine is an acylated cytidine, not an acylated deoxycytidine. Therefore, even assuming for the sake of argument that it would have been obvious to substitute acylated deoxycytidine for free deoxycytidine, the patentability of claim 16 would be unaffected.

Turning to claim 17, as admitted in the action (page 8), Bhalla fails to describe the use of acylated deoxycytidines in place of free deoxycytidine. In an attempt to cure this deficiency, the Examiner relies on Von Borstel in view of the mention in that disclosure of acylated deoxycytidine. However, a person of ordinary skill would **not** have been motivated to arrive at the presently claimed method on the basis of the combined disclosures of Bhalla and Von Borstel, since there is no suggestion in Bhalla, taken alone or in combination with Von Borstel, of the methodology as claimed in this case.

Claims 20-21 are directed to a method for preventing or treating toxicity due to a pyrimidine nucleoside analog (e.g. prodrugs of arabinosyl cytosine) comprising administering to an animal an acylated derivative of cytidine or deoxycytidine and an inhibitor of cytidine deaminase (e.g. tetrahydrouridine). At page 9 of the Action, it is admitted that neither Bhalla nor Von Borstel disclose a cytidine deaminase inhibitor. In order to overcome this deficiency, the Examiner relies on U.S. Patent 4,017,606 to Hanze. This rejection is respectfully traversed.

The evaluation of patentability or unpatentability under 35 U.S.C. § 103 is based on factual inquiries, one of which is the content of the prior art. As stated by the Supreme Court in *Graham v. John Deere*:

> "Under § 103, the scope and content of the prior art are to be determined.... Against this background, the obviousness or nonobviousness of the subject matter is determined." *Graham v. John Deere Co.*, 383 U.S. 1, 27, 148 USPQ 459, 467 (1966)

The rejection on page 9 of the action is based on the incorrect assertion that Hanze teaches increasing free cytidine levels with an inhibitor of cytidine deaminase. It is this alleged teaching that is relied on as providing the motivation to combine the cytidine deaminase inhibitor of Hanze with the acylated deoxycytidine of von Borstel. In this regard the rejection states:

> "Hanze et al. does disclose tetrahydrouridine as a cytidine deaminase inhibitor (column 5, lines 42-61) and its use to prevent the degradation of a cytidine nucleoside analog. It would have been *prima facie* obvious to the person of ordinary skill in the art at the time of the invention to have replaced free deoxycytidine with a combination of acylated deoxycytidine and tetrahydrouridine. One of ordinary skill would have been motivated to combine an acylated deoxycytidine and tetrahydouridine in order to obtain even higher levels of free cytidine in serum and tissue which would create even more reduction in the toxicity of cytidine arabinose or any other pyrimidine nucleoside analog." (page 9)

As seen from the above-quoted passage, the rejection rises and falls on the premise that Hanze teaches that a cytidine deaminase inhibitor would result in "even higher levels of free cytidine in serum and tissue". This does not occur.

The Action does not point to any explicit teaching of Hanze or other prior art in support of the position that administering an inhibitor of cytidine deaminase would increase levels of free cytidine. Instead, the supposed expectation of increasing *in vivo* cytidine levels by administering a deoxycytidine deaminase inhibitor appears to be based on the more general assumption that inhibiting any given degradative enzyme would be expected to increase the *in vivo* levels of the substrate of that enzyme. While that assumption may be true in some cases, it is not true in others. For example, it was

known that inhibiting uridine phosphorylase by administering its inhibitor 5-benzylacyclouridine (BAU) had no effect on plasma uridine in monkeys. This can be seen from the enclosed abstract of Davis, et al., Biochem. Pharmacol. (1993) 45(1): 173-81, which states:

> "In the monkey, BAU (30 mg/kg, i.v.) had no effect on plasma uridine despite the presence of 10-100 microM BAU levels in plasma for 1.5 hr." (Abstract of Davis, et al., "Species-dependent differences in the biochemical effects and metabolism of 5-benzylacyclouridine." (Biochem. Pharmacol. (1993) 45(1): 173-81)

As seen from the above-quoted passage, administering an inhibitor of a degradative enzyme does not necessarily lead to increased plasma levels of the substrate of that enzyme. Therefore, the person of ordinary skill in the art would not have had a reasonable expectation that administering an inhibitor of any given enzyme such as an inhibitor of deoxycytidine deaminase would lead to increased *in vivo* levels of the substrate of that enzyme. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). A *prima facie* case of unpatentability under 35 U.S.C. § 103 has not been made.

In regard to the evidence of unexpected results provided in the originally filed application, the Examiner has argued on page 9 of the action that pages 42-44 of the specification contain conclusory statements about the compounds of the invention and that Example 6 does not present a result not contemplated by the prior art. The Examiner also states that the factual evidence set forth is not commensurate with the scope of the claims, and is consistent with the Examiner's motivation theory.

In response, Example 6 provides *in vivo* evidentiary support of efficacy of the present invention. Table 13 presents the actual *in vivo* data, and clearly shows

unexpected tumor regression with minimal mortality as compared to the control group. These results are unexpected and consistent with the invention as claimed. Since the results are unexpected, they could not have been "contemplated by the prior art", contrary to the Examiner's assertion. While it is true that Table 13 shows that uridine administered i.p. was marginally more effective at tumor regression as compared to TAU administered p.o., the difference in mortality rates is entirely unexpected.

Based on the above, it is clear that the various combinations of references relied upon by the Examiner do not give rise to a *prima facie* case of obviousness of any of the currently pending claims. Withdrawal of all of the outstanding obviousness rejections is accordingly respectfully requested.

III. WITHDRAWAL OF FINALITY OF ACTION

The outstanding action has been made final. It is believed that this is premature and that the finality of the action should be withdrawn.

In its Remand to the Examiner mailed April 30, 2002, the Board of Patent Appeals and Interferences *inter alia* stated that the rejections in the previous final rejection "were not susceptible to meaningful review". The Board stated that the Examiner should clearly provide an indication of the motivation to combine the teachings of the cited references. Moreover, the Board noted that the Examiner had not considered the evidence of unexpected results and had not responded to the applicants' comments relating to the Kralovansky and Kelsen references. In effect, the Board found that the prior rejection was incomplete and required the issuance of a further action with additional commentary from the Examiner.

In the outstanding action, the Examiner has provided new grounds to support the obviousness rejections. This is the **first** time that the applicants have seen this reasoning and, as such, the action should have been made non-final. The applicants are entitled to respond to what now amounts to new obviousness rejections in the context of a non-final rejection, without being under the strictures of final rejection. It is believed, therefore, that the finality of the outstanding action is premature and should be withdrawn. Such action is respectfully requested.

Favorable action is awaited.

Respectfully submitted,

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Attachments: PTO-1449; copy of Kralovansky and Calabresi as listed on the PTO-1449; Davies abstract